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| EXAMINER | |
|---|---|
| ALAWADI, SARAH | |
| ART UNIT | PAPER NUMBER |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/587,456 | MAGDASSI ET AL. | |
| | Examiner | Art Unit | |
| | SARAH AL-AWADI | 1619 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on *04/28/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *41-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

## RESPONSE TO REMARKS

Applicant's election without traverse of Group I, claims 41-53 in the reply filed on 04/28/2009 is acknowledged. Claims 54-64 have been withdrawn from consideration.

## PRIORITY

Applicant's claim to foreign priority of PCT/IL05/000093 which has an effective filing date of January 28, 2004 has been acknowledged. Applicant's have submitted an English translation.

## INFORMATION DISCLOSURE STATEMENT

No Information Disclosure Statements (IDS) have been submitted.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 42 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear what is meant by "single species" of hydrophilic polymer. For the purposes of examination, the Examiner broadly and reasonably interprets "single species" to include that of polymers that are made up of the same reoccurring monomers such as polyvinyl pyrrolidone.

Claims 43-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 43 and 44 are rejected for reciting improper Markush language. Claims 43 and 44 recite the term “selected from.” Claims 43-44 requires the addition of the word/phrase “selected from the group consisting of.” Furthermore the “and” that ends the Markush group in claims 43- 44 needs to be replaced by “or” for Markush claims. See MPEP 2173.05(h).

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required

feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 44 recites the broad recitation anti-alzheimer agents and the claim also recites galantamine which is the narrower statement of the range/limitation. Galantamine is a species of an anti-alzheimer drug. The claim also recites particular hydrophobic drugs such as simvastatine, risperidone ect. which are followed by a broader genus of drugs such as statines, anti-Alzheimer, anti-epileptic, and anti-parkinsonian.

Claim 47 recites the limitation, "the drug delivery system according to claim 41 wherein the crosslinker is a multivalent cation." There is insufficient antecedent basis for this limitation in the claim because claim 41 does not recite a crosslinker.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 41-43, and 50 are provisionally rejected on the ground of statutory type double patenting as being unpatentable over claims 6-12 copending Application No. 10/590621 further in view of Staniforth et al. United States Patent Application 2004/0265374 and Jonghwi Lee, Journal of Pharmaceutical Sciences, vol. 92, NO. 10, October 2003. (see 892 form)

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims presented in the '621 application are obvious variants, if not anticipatory, of the currently presented claims.

Claims 41-43 of the current application are directed towards a drug delivery system comprising nanoparticles or microparticles of a poorly soluble drug dispersed in a polymeric hydrophilic bead and a disintegrate mixed with the bead. The polymeric bead consists of a hydrophilic polymer, and can be selected from the group consisting of a polysaccharide polymer, a synthetic polymer, and a protein. The polymeric bead can be selected to be gelatin.

Copending claims 6-12 are obvious over the current application because they are directed towards a polymer delivery system of poorly soluble drugs such as quinazolinone (formula I). The delivery system can contain a hydrophilic polymer such as a polysaccharide and protein of which gelatin can be selected. (claim 11-12).

The copending application does not mention the addition of a disintegrate to the drug delivery system, or that the drugs are in microparticle or nanoparticle form. However, it would have been prima facie obvious to the skilled artisan to add a disintegrate to the composition because Staniforth et al. teaches that disintegrants are often included in compositions to ensure an acceptable disintegration rate. (paragarph 0009) Furthermore it would have been obvious to

make the insoluble drugs in nanoparticle or microparticle sizes because Jonghwi Lee teaches that reducing the particle size of an active pharmaceutical ingredient into microparticles or nanoparticles is an effective method to improve the bioavailability of relatively insoluble drugs. (page 1) As evidenced by Jonghwi Lee is well known in the art that reducing the particle size of drugs results in improved bioavailability.

Thus the claims presented in the '621 application are obvious variants, if not anticipatory, of the currently presented claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 41-43 and 46, rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper et al. WO2004/011537 further in view of Jonghwi Lee, Journal of Pharmaceutical Sciences, vol. 92, No. 10, October 2003. (see 892 form)

Claim 41 recites a drug delivery system comprising nanoparticles or microparticles of a poorly soluble drug dispersed in a polymeric hydrophilic bead and a disintegrate mixed within.

Cooper et al. teaches a drug delivery system comprising a polymer hydrophilic bead (poly vinyl alcohol) and a disintegrate (Sodium dodecyl sulphate) (Table 2, page 20) Cooper recites that hydrophobic active ingredients can be incorporated into the beads. (claim 19)

Claim 42 recites the drug according to claim 41 wherein the polymeric bead consists essentially of a single species of hydrophilic polymer. Cooper et al. teaches that the polymer bead can consist of poly vinyl alcohol which is a hydrophilic polymer. (page 8)

Claim 43 recites a drug delivery system of claim 42 wherein the polymer bead is selected from a polysaccharide polymer, a synthetic polymer, and a protein. Cooper et al. teaches an embodiment wherein the polymer bead can be polyvinylpyrrolidone. (table 7)

Claim 46 recites a drug deliver system according to claim 41, further comprising a crosslinker. Cooper et al. teaches that the porous beads can be crosslinked to enhance mechanical strength by cross linking agents such as 2,4-tolylene diisocynate. (see page 7)

Cooper et al. does not expressly teach that the poorly soluble drug is a nanoparticle or a microparticle dispersed in the polymer bead.

Jonghwi Lee teaches that reducing the particle size of an active pharmaceutical ingredient such as into microparticles or nanoparticles is an effective method to improve the bioavailability of relatively insoluble drugs. (page 1)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate the hydrophobic drug of Cooper et al. into a microparticle or nanoparticle form. One would have been motivated to do so because Jonghwi Lee teaches mixing microparticles or nanoparticles with beads. (page 3) Furthermore, as evidenced by Jonghwi Lee, it is well known in the art that reducing the particle size of drugs results in improved bioavailability.

Claims 41-44, and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soon-Shiong et al. United States Patent Application 2002/0090399 further in view of Desai et al. United States Patent Application 2007/0092563.

Claim 41 recites a drug delivery system comprising nanoparticles or microparticles of a poorly soluble drug dispersed in a polymeric hydrophilic bead and a disintegrate mixed within.

Soon-Shiong et al. teaches an embodiment with microcapsules of active agents wherein the outer layer can be polyionically crosslinked. Absent evidence to the contrary, the Examiner interprets beads to include that of polymeric hydrophilic micro or nanocapsules, furthermore Soon-Shiong teaches microcapsule are an example of beads. (see method of testing microcapsules paragraph 0147). Examples of polymers that can be polyionically crosslinked are hydrophilic polymers such as polyvinylpyridine. (paragraph 0075) Soon-Shiong further teaches that EDTA can be added to the microcapsule to disrupt the ionic crosslinking, thus acts like a disintegrate. (paragraph 0116) Soon-Shiong teaches that various drugs can be used with the polymer beads, one of which is an antiparkinson agent such as ethosuximide. (paragraph 0049) Ethosuximide (as evidenced by paragraph 0106 of Desai et al.) is known as a water insoluble (poorly soluble) drug.

Claim 42 recites a drug according to claim 41, wherein the polymeric bead consists essentially of a single species of hydrophilic polymer. Soon-Shiong teaches hydrophilic polymers can be used for the microcapsules such as polyvinylpyridine. (paragraph 0075)

Claim 43 recites that the drug delivery system of claim 41 can comprise a polymeric bead that is a synthetic polymer. As shown above, Soon-Shiong teaches polymer beads can include that of polyvinylpyridine which is an example of a synthetic polymer.

Claim 44 recites that the drug delivery system of claim 41 wherein the poorly soluble drug can include that of anti parkinson agents. As stated above, Soon-Shiong teaches that various drugs can be used with the polymer beads, one of which is an antiparkinson agent such as ethosuximide (paragraph 0049) Ethosuximide (as shown by paragraph 0106 of Desai et al.) is known as a water insoluble (poorly soluble) drug.

Claim 46 recites a drug delivery system according to claim 41, further comprising a crosslinker, and claim 47 recites wherein the crosslinker is a multivalent cation. Soon-Shiong et

al. teaches that crosslinkers such as multivalent cations can be present which yield crosslinked microcapsules. (paragraph 0103)

Claim 48 recites that the drug delivery system of claim 41 contains a disintegrate that is capable of breaking the crosslinking by replacing or chelation of the crosslinking multivalent cation. Until some material difference(s) in the properties of the composition are demonstrated, said limitation is considered by the Examiner to be directed toward the drug delivery system comprising a disintegrate which is instantly claimed. Furthermore, Soon-Shiong et al. teaches that disintegrates such as EDTA chelates the cations to disrupt ionic crosslinking the microcapsule. (paragraph 0116)

Claim 49 recites a drug delivery system according to claim 41, wherein the disintegrate is a calcium chelator. Soon-Shiong et al. teaches that disintegrates such as EDTA chelates the cations such as calcium, zinc, barium, strontium ect. to disrupt ionic crosslinking the microcapsule. (paragraph 0069 and 0116)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to create drug delivery systems which comprise hydrophobic drugs and hydrophilic polymers and a disintegrant because the combined teachings of Soon-Shiong et al. and Desai et al. suggest the combination with hydrophobic drugs. One would have been motivated to create these drug systems because Soon-Shiong teaches that they provide good mechanical strength and an enhanced control over the release rates of drugs. (paragraph 0013 and 0007)

Claims 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Soon-Shiong et al. United States Patent Application 2002/0090399 further in view of Jonghwi Lee, Journal of Pharmaceutical Sciences, vol. 92, No. 10, October 2003. (see 892 form)

Claim 51 recites a drug delivery system comprising an active ingredient dispersed within a crosslinked polymeric bead wherein the crosslinking is by a cation such as copper, and wherein the drug delivery system further comprises a chelator of calcium as a disintegrate. Claim 52 recites that the active ingredient is a poorly soluble drug. Soon-Shiong et al. teaches an embodiment with microcapsules of active agents wherein the outer layer can be polyionically crosslinked. Absent evidence to the contrary, the Examiner interprets beads to include that of polymeric hydrophilic micro or nanocapsules, furthermore Soon-Shiong teaches microcapsule are an example of beads. (see method of testing microcapsules paragraph 0147). Examples of polymers that can be polyionically crosslinked are hydrophilic polymers such as polyvinylpyridine. (paragraph 0075) Soon-Shiong further teaches that EDTA can be added to the microcapsule to disrupt the ionic crosslinking, thus acts like a disintegrate. (paragraph 0116) Soon-Shiong teaches that various drugs can be used with the polymer beads, one of which is an antiparkinson agent such as ethosuximide. (paragraph 0049) Ethosuximide (as evidenced by paragraph 0106 of Desai et al.) is known as a water insoluble (poorly soluble) drug. Regarding the disintigrate, Soon-Shiong et al. teaches that EDTA chelates cations such as calcium, zinc, barium, strontium ect. to disrupt ionic crosslinking of the microcapsule. (paragraph 0069 and 0116)

Soon-Shiong does not expressly teach that the poorly soluble drug is in the form of nanoparticles.

Jonghwi et al. teaches that reducing the particle size of an active agent improves the bioavailability of relatively insoluble drugs.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to minimize the microparticles of Soon-Shiong et al. to form nanoparticle systems because Jonghwi Lee et al. teaches an advantage such as increased bioavailibity. One would have been motivated to reduce the particle size from microns to nanometers because Jonghwi Lee.teaches that doing so increases the surface area which greatly increases the dissolution rate.

Claims 41-45 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Desai et a. WO/2000/071079 further in view of Catron et al. US Patent 6,146,671.

Claim 41 recites a drug delivery system comprising nanoparticles or microparticles of a poorly soluble drug dispersed in a polymeric hydrophilic bead and a disintegrate mixed within, and claim 42 recites that the drug according to claim 41 wherein the polymeric bead consists essentially of a single species of hydrophilic polymer.

Desai '079 teaches water insoluble active agents in nanoparticle or microparticle form (page 8, line 11) that are encased in a polymeric shell formulated from a biocompatible polymer. (page 1, lines 15-16) The polymer shell has a dispersing agent (disintegrate) which can dissolve the active agent. (page 1, lines 21-22) Desai further describes such polymers can be of polyvinyl alcohol (page 17, line 22) which is known to the skilled artisan to be a hydrophilic polymer, and that the delivery system can include that of beads. (page 15, line 19)

Regarding claim 43 which recites that the polymeric bead is selected from a polysaccharide polymer, a synthetic polymer, and a protein, Desai '079 teaches that synthetic polymers can be used such as polyvinyl pyrrolidinone. (page 32, line 17)

Claim 44 recites that the drug delivery system according to claim 41 comprises a poorly soluble drug which can be selected to be an anti-parkinsonian agent. Desai '079 teaches various drugs can be used with the polymer beads, one of which is an antiparkinson agent such as ethosuximide. (column 27, line 15) Ethosuximide (as evidenced by paragraph 0106 of Desai et al.) is known as a water insoluble (poorly soluble) drug.

Claim 45 recites the drug delivery system of claim 41, wherein the nanoparticles are in an amorphous, noncrystalline form which enhances dissolution of the drug. Desai '079 teaches that the drug can be in amorphous form, which would lead to greater ease of dissolution and absorption resulting in better bioavailability. (page 10, lines 28-29 and page 11 lines 1-2)

Desai '079 does not expressly teach that the beads are gelatin beads. (as recited in instant claim 50)

Catron et al. teaches the preferred use gelatin beads and suggests that gelatin beads act to protect the composition. (column 7, lines 7-8 , figure 2, and abstract)

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to select gelatin beads as the hydrophilic beads of Desai '079. One would have been motivated to do so because the prior art teaches gelatin as a preferred suitable polymer bead.

## *Correspondence*

Any inquiry concerning this communication or earlier communications from the

examiner should be directed to Sarah Al-Awadi whose telephone number is (571) 270-7678. The examiner can normally be reached on 9:30 am - 6:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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